Glutathione synthetase deficiency

Metabolic disorder carrying a risk of metabolic acidosis and low bicarbonate if gastroenteritis occurs

Label

1 CLINICAL PRESENTATION AND TREATMENT

Glutathione synthetase deficiency presents as metabolic acidosis in the neonate, haemolytic anaemia and often neurological disorders. Positive diagnosis is made by major increase of urinary 5-oxoproline (pyroglutamic acid) on the organic acids urine analysis. Mutation analysis for glutathione synthetase (*GSS*) confirms the diagnosis (autosomal recessive pattern).

Treatment involves:

- Correction of the acidosis (sodium bicarbonate / sodium citrate, potentially at high doses).
- Antioxidants
  1. Ascorbic acid (vitamin C) 50 to 60 mg/kg/day. If there is no commercially available oral form, use injectable LAROSCORBINE 1g/5mL, given *orally*.
  2. Vitamin E (tocopherol) *orally*; contributes to granulocyte function.
     Several formulations and dosages currently available:
     - VITAMIN E 100 mg/mL, oral suspension
     - TOCO 500 mg, soft capsule; TOCOLION 500 mg, soft capsule: 10 mg/kg/day (100 to 300 mg/day). Since soft capsules cannot be split, give the whole capsule for patients weighing over 35 kg. Maximum dose = 500 mg/day.
- Avoid drugs known to induce haemolysis, for example in patients with glucose-6-phosphate dehydrogenase deficiency (notably phenobarbital, acetylsalicylic acid and sulfonamides).
- Correct haemolytic anaemic if present (folic acid supplements and transfusion if necessary).

2 IF VOMITING / DIARRHOEA OR INTERCURRENT DISEASE

- **If the patient has gastroenteritis, it is important to correct metabolic acidosis and bicarbonate deficit.**
- Urgent serum electrolytes and blood gases ; look for acute haemolysis: regenerative anaemia (FBC, reticulocytes, LDH, haptoglobin, AST, total/free bilirubin, haemoglobinuria)

- **Infusion of 1.4% isotonic sodium bicarbonate**
  - Continuous IV, replacing usual oral intakes
  - plus IV over 3 hours, to correct the bicarbonate deficit

  Bicarbonate deficit (mmol) = 0.4 x body weight (kg) × (24 – serum bicarbonate [mmol/L])
  NB 1 g of sodium bicarbonate contains 11.9 mmol of HCO_3^- and 11.9 mmol of Na^+

Look up the emergency

- **Infusion of glucose + standard electrolytes according to patient weight and age.**

3 MONITORING

- **Regularly check serum bicarbonate, electrolytes, and pH every 4 to 6 hours to adjust the dose of bicarbonates IV; check the FBC** (and reticulocyte count) **every 12 hours.**
- Also monitor serum bicarbonate after restarting oral therapy.

4 PATHOPHYSIOLOGY

Glutathione synthetase deficiency. Glutathione has multiple functions in the cell, particularly acting as a NADP/NADPH-dependent redox buffer. One major regulatory mechanism in the glutathione cycle is the negative feedback action exerted by glutathione on gamma-glutamylcysteine synthetase. When there is a glutathione synthesis deficiency, the increased activity of gamma-glutamylcysteine synthetase leads to accumulation of a glutathione cycle intermediate, 5-oxoproline.
Glutathione synthetase deficiency presents as neonatal metabolic acidosis, haemolytic anaemia and neurological disorders (absent in mild forms). The diagnosis is made on urinary organic acids, showing a major urine excretion of 5-oxoproline (pyroglutamic acid).

Treatment involves:
- Correction of the acidosis (sodium bicarbonate / sodium citrate),
- Antioxidants: vitamin C and vitamin E

5 DRUG CONTRAINDICATIONS

Contraindication:
- Despite its efficacy as an antioxidant, N-acetylcysteine (200 mg/kg/day) is no longer recommended for these patients because, when glutathione synthetase deficiency exists, it leads to an accumulation of cysteine with a risk of neurotoxicity.
- Avoid drugs which are liable to cause haemolysis where glucose-6-phosphate dehydrogenase deficiency exists. **https://ansm.sante.fr/actualites/medicament-et-deficit-en-g6pd-lansm-actualise-le-referentiel**

6 ACTION TO BE TAKEN BEFORE PLANNED GENERAL ANAESTHESIA

- Continue treatment with bicarbonate - see above.
- Anaesthetics: the following can be cited:
  - https://www.orphananesthesia.eu/en/rare-diseases/published-guidelines/glucose-6-phosphate-dehydrogenase-deficiency
  - an example of using sevoflurane and sulfentanil which did not cause haemolysis in a G6PD patient. Ketamine, isoflurane and sevoflurane could be used in these patients; the concomitant use of diazepam or midazolam with sevoflurane or isoflurane is contraindicated, because it increases the risk of severe haemolysis. Cicvaric *et al.* Management of Anesthesia and Perioperative Procedures in a Child with Glucose-6-Phosphate Dehydrogenase Deficiency. J Clin Med. 2022.
  - in particular, seven drugs cause problems: dapsone, methylthioninium chloride (methylene blue), nitrofurantoin, phenazopyridine, primaquine, rasburicase and tolonium chloride (toluidine blue). The study did not find evidence supporting avoidance of other drugs, at the usual therapeutic doses in G6PD patients. Youngster *et al.* Medications and Glucose-6-Phosphate Dehydrogenase Deficiency. Drug Safety. 2010.

NUMBERS AND MEDICAL SPECIALISTS

To be completed by each department

At night, only medical teams can call in emergency situations, and only if the emergency certificate has not been understood or if the clinical state or test results are worrying. As far as possible, make calls before nighttime.
Secretarial issues must be dealt with via the medical secretariat during the week, or by email addressed to the patient's metabolic medicine specialist.
Certificate issued on Dr